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(54) Title: **COMBINATION OF A TAXANE AND A CYCLIN-DEPENDENT KINASE**

(57) Abstract: A pharmaceutical composition comprised of Taxol[®], Taxotere[®], or derivatives and a cyclin-dependent kinase is described, as well as a form of administration wherein the taxane is given intermittently and the cyclin-dependent kinase is given repeatedly within the same cycle.

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COMBINATION OF A TAXANE AND A CYCLIN-DEPENDENT KINASE

The present invention relates to combinations of Taxol[®], Taxotere[®] and their analogues and other compounds which are therapeutically useful in the treatment of neoplastic diseases. More especially, the invention relates to combinations of Taxol[®], Taxotere[®] and their analogues with cyclin-dependent kinases.

Taxanes and taxoids constitute a family of naturally occurring diterpene compounds including a potent antitumor drug, paclitaxel. Paclitaxel (Taxol[®]), originally isolated from the bark of the Pacific Yew tree (*Taxus brevifolia*), has been shown to be highly effective in adjuvant and neo-adjuvant therapies for patients with breast and ovarian cancers. More recently, its semisynthetic analogue, docetaxel (Taxotere[®]), has also been found effective in breast cancer chemotherapy, which has expanded the number of diseases sensitive to this class of antitumor drugs, including lung and colon cancers. Both Taxol[®] (paclitaxel) and Taxotere[®] (docetaxel) bind to tubulin, inhibit microtubule disassembly, and impair mitosis, thereby blocking progression through M phase of the cell cycle and facilitating apoptosis.

In spite of the undoubted overall clinical success of the taxoids, some tumors display resistance to these drugs. This drug resistance may be an innate feature of a tumor, or may develop in the tumor over time. Three main mechanisms of drug-resistance have been reported: (i) point mutations of the tubulin gene, (ii) selection of tubulin isoforms with low binding to taxanes, and (iii) expression of the multidrug-resistance (MDR) phenotype mediated by the P-glycoprotein (P-gp) efflux pump encoded by the *mdr1* gene. Mechanism (iii) may explain the innate resistance to Taxol[®] and Taxotere[®] in tumors that often inherently express P-gp, such as colon and kidney cancers.

The combinations or associations according to the invention enable the phenomena of pleiotropic resistance or "multi-drug resistance" to be avoided or delayed.

The preparation of Taxol[®], Taxotere[®] and their derivatives form the subject, for example, of European Patents EP 0,253,738 and EP 0,253,739 and International Application PCT WO 92/09,589.

It has now been found, and this forms the subject of the present invention, that the efficacy of Taxol[®], Taxotere[®] and their analogues may be

considerably improved when they are administered in combination with at least one substance which is therapeutically useful in anticancer treatments and has a mechanism identical to or different from these taxanes.

Among substances which may be used in association or in combination with Taxol[®], Taxotere[®] or their analogues, there may be mentioned enzymes such as L-asparaginase and cyclin-dependent kinases, such as flavopiridol, quercitin and genistein. Various agents such as biological response modifiers or growth factor inhibitors, such as interferons or interleukins, may also be used.

Since the activity of the products depends on the doses used, it is possible to use higher doses and to increase the activity while decreasing the toxicity phenomena or delaying their onset by combining growth factors of the haematopoietic type such as G-CSF or GM-CSF or certain interleukins with Taxol[®], Taxotere[®], their analogues or their combinations with other therapeutically active substances.

More especially, the invention relates to combinations of Taxol[®], Taxotere[®] and their analogues with the cyclin-dependent kinase, flavopiridol.

Cyclin-dependent kinases (CDKs) are important regulators that control the timing and coordination of the cell cycle. CDKs form reversible complexes with their obligate cyclin partners to control transition through key junctures in the cell cycle. For example, the activated CDK4-cyclin D1 complex controls progression through the G1 phase while the CDK1-cyclin B1 complex controls entry into the mitotic phase of the cell cycle. Endogenous cyclin dependent kinase inhibitory proteins (CKIs) are known which bind either the CDK or cyclin component and inhibit the kinase activity. In many tumors such as melanomas, pancreatic and esophageal cancers, these natural CKIs are either absent or mutated. Thus, selective CDK inhibitors may prove to be effective chemotherapeutic agents.

Flavopiridol (*cis*-5,7-dihydroxy-2-(2-chlorophenyl)-8-[4-(3-hydroxy-1-methyl)-piperidinyl]-1-benzopyran-4-one) is a synthetic flavone that has been shown to have antitumor activity against various tumor cells lines such as human lung carcinoma, breast carcinoma, and also inhibits tumor growth in xenograft models. It has been shown to induce arrest in both the G1 and G2 phases of the cell cycle. Flavopiridol is a potent and selective inhibitor of the CDKs, and its antitumor activity is related to its CDK inhibitory activity. Studies have shown that its tumor cell growth inhibitory activity occurs in a cell cycle specific manner. See Bioorg. & Med. Chem. Letters 10:1037-1041(2000).

Taxotere® and flavopiridol have differing mechanisms which can improve the efficacy of each. The improved efficacy of a combination according to the invention may be demonstrated by determination of the therapeutic synergy. A combination manifests therapeutic synergy if it is therapeutically superior to one or other of the constituents used at its optimum dose (T.H. Corbett et al., Cancer Treatment Reports, 66: 1187 (1982)).

To demonstrate the efficacy of a combination, it may be necessary to compare the maximum tolerated dose of the combination with the maximum tolerated dose of each of the separate constituents in the study in question. This efficacy may be quantified, for example, by the \log_{10} cell kill, which is determined according to the following formula:

$$\log_{10} \text{ cell kill} = T - C \text{ (days)} / 3.32 \times T_d$$

in which $T - C$ represents the time taken for the cells to grow, which is the mean time in days for the tumors of the treated group (T) and the tumors of the treated group (C) to have reached a predetermined value (1 g for example), and T_d represents the time in days needed for the volume of the tumor to double in the control animals (T.H. Corbett et al., *Cancer*, 40, 2660-2680 (1977); F.M. Schabel et al., *Cancer Drug Development, Part B, Methods in Cancer Research*, 17, 3-51, New York, Academic Press Inc. (1979)). A product is considered to be active if \log_{10} cell kill is greater than or equal to 0.7. A product is considered to be very active if \log_{10} cell kill is greater than 2.8.

The combination, used at its own maximum tolerated dose, in which each of the constituents will be present at a dose generally not exceeding its maximum tolerated dose, will manifest therapeutic synergy when the \log_{10} cell kill is greater than the value of the \log_{10} cell kill of the best constituent when it is administered alone.

The efficacy of the combinations on solid tumors may be determined experimentally in the following manner:

The animals subjected to the experiment, generally mice, are subcutaneously grafted bilaterally with 30 to 60 mg of a tumor fragment on day zero. The animals bearing tumors are mixed before being subjected to the various treatments and controls. In the case of treatment of advanced tumors, tumors are allowed to develop to the desired size, animals having insufficiently developed tumors being eliminated. The selected animals are distributed at random to undergo the treatments and controls. Animals not bearing tumors may also be subjected to the same treatments as the tumor-bearing animals in

order to be able to dissociate the toxic effect from the specific effect on the tumor. Chemotherapy generally begins from 3 to 22 days after grafting, depending on the type of tumor, and the animals are observed every day. The different animal groups are weighed 3 or 4 times a week until the maximum weight loss is attained, and the groups are then weighed at least once a week until the end of the trial.

The tumors are measured 2 or 3 times a week until the tumor reaches approximately 2 g, or until the animal dies if this occurs before the tumor reaches 2 g. The animals are autopsied when sacrificed.

The antitumor activity is determined in accordance with the different parameters recorded in Tables I and II.

For a study of the combinations on leukemias, the animals are grafted with a particular number of cells, and the antitumor activity is determined by the increase in the survival time of the treated mice relative to the controls. The product is considered to be active if the increase in survival time is greater than 27%, and is considered to be very active if it is greater than 75% in the case of P388 leukemias.

In the Examples which follow, mice were grafted with mammary adenocarcinoma MA 13/C and treated with combinations of Taxotere® and flavopiridol having different schedules of administration and different modes of administration. Both Taxol and Taxotere, as well as flavopiridol may be administered orally as well as intravenously. Some of these schedules show clear therapeutic synergy.

Additional objects and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention as claimed.

Example 1

In order to determine the activity of each constituent of the combination, Taxotere® and flavopiridol were given alone to MA 13/C bearing mice. Taxotere® was administered intravenously on days 15 and 21; the dose on each day was

30 mg/kg for a total dosage of 60 mg/kg. Used alone, this dosage resulted in a \log_{10} cell kill of 4.7 and a complete response in all 5 of the mice so treated. Administration of flavopiridol alone on days 15 and 21 in a dose of 6 mg/kg each day, or a total dosage of 12 mg/kg, resulted in no complete responses in the 5 mice tested.

The compounds were then combined in two ways and tested in an intermittent schedule. In the first combination, flavopiridol was given first on days 15 and 20 (total dosage 9 mg/kg) and Taxotere® was given on the following days 16 and 21 (total dosage 45 mg/kg). When given in this fashion, the \log_{10} cell kill was 5.5 and resulted in 5 of 5 complete responses in the mice treated. In this intermittent schedule, the \log_{10} cell kill was better than Taxotere® given alone and still resulted in 5 of 5 complete responses despite the fact that 25 % less Taxotere® and 25 % less flavopiridol were administered in this combination than in the control.

When the constituents of the combination were reversed and Taxotere® was given first on days 15 and 20 and flavopiridol was given on days 16 and 21 in the same amounts, the \log_{10} cell kill was slightly less than Taxotere® alone, but again there were 5 of 5 complete responses. Table 1 illustrates these results and shows that the combination of flavopiridol and Taxotere® administered in 25 % lesser amounts had an efficacy similar to Taxotere® alone.

Table I

Flavopiridol- Taxotere® Combination in MA13/C bearing mice : 24 hours apart

| IV Agent | Schedule | HNTD (DT) mg/kg | | % bwl (nadir) | lck | Comments |
|---------------------------|----------|--------------------|---------------|------------------|-----|---------------|
| | | Docetaxel | Flavo | | | |
| Taxotere® | 15,21 | 30.0 (60.0) | - | 8 (27) | 4.7 | 5/5 CR HDE |
| Flavopiridol | 15,21 | - | 6.0 (12.0) | 6 (16) | 0.4 | 0/5 CR |
| Combination 24 h apart | | | | | | |
| Flavo 1 st | 15,20 | 22.5 | 4.5 | 7 (22) | 5.5 | 5/5 CR HDE |
| Taxotere | 16,21 | (45.0) | (9.0) | | | |
| Taxotere 1 st | | 22.5 (45.0) | 4.5 (9.0) | 7 (25) | 4.4 | 5/5 CR HDE |

Td = 2.2 days ; time for control to reach 1 g = 20.3 days ; median burden at start of therapy = 130-160 mg

- 5 CR = complete response ; IV = intravenous ; bwl = body weight loss at nadir ; (DT) = total dose ;
HNTD = highest non-toxic dose ; lck = log₁₀ cell kill

Example 2

The days on which flavopiridol was administered were increased, and it was discovered that when the MA 13/C bearing mice were exposed to similar
10 doses of flavopiridol given over 8 days in a 10 day cycle while Taxotere® was given on the first and last day of the ten day cycle, there was clear synergy.

Table 2 below gives the highest non-toxic total dose of each component alone - 96.8 mg/kg of Taxotere® and 23.2 mg/kg of flavopiridol. When the constituents were administered in combination, with Taxotere® being
15 administered on days 14 and 23 and flavopiridol on days 14-17 and 20-23, three combinations were clearly synergistic and a fourth was equal in efficacy to Taxotere® alone. All four combinations resulted in 6 of 6 complete responses; i.e., 100 % complete responses.

A 3-arm dose-response study was performed in C3H/HeN mice bearing
20 measurable tumors at start of therapy (230 mg). The model chosen was a murine mammary adenocarcinoma MA13/C, selected on the basis of its

chemosensitivity to docetaxel. Mice were treated with Flavo (i.e. once a day, day 14 to 17, and day 20-23 post tumor implantation), or docetaxel (i.e. on days 14 and 23), or their combination. Results: At the highest non-toxic dose (HNTD, 2.9 mg/kg/dose, total dose of 23.2 mg/kg), Flavo administered IV as a single agent was inactive with a - 0.4 log cell kill net (log cell kill net = tumor growth delay - treatment duration / 3.32 x tumor doubling time), and no complete regression (CR). The HNTD of docetaxel alone (48.1 mg/kg/injection, total dose of 96.8 mg/kg) was found very active (3 log cell kill net, 6/6 CR). Clear synergy was obtained at the highest non-toxic combination (Flavo at 1.93 mg/kg/dose and docetaxel at 53.2 mg/kg/injection) with a 7.6 log cell kill net and 6/6 CR. This combination was well tolerated inducing a 13 % body weight loss at nadir occurring 6 days post last treatment. Synergy was retained on 2 additional lower dose levels compared to docetaxel HNTD. This synergy was also observed when Flavo was administered orally.

TABLE II

Flavopiridol - Taxotere® Combination
Mammary adenocarcinoma MA13/C "repeated exposure"

| IV agents mg/kg/dose (total dose) | | % bwl (nadir) | lck Gross | CR | Comments |
|--------------------------------------|------------------------------|------------------|--------------|-----|----------|
| Taxotere d14,23 | Flavopiridol d14-17,20-23 | | | | |
| 78.1 (156.2) | - | 20 (29) | - | - | 2/6 DD |
| 48.1 (96.8) | - | 8 (28) | 4.4 | 6/6 | HNTD |
| - | 4.8 (38.4) | >20 | - | - | 4/5 DD |
| - | 2.9 (23.2) | 3 (18) | 1.0 | 0/6 | HNTD |
| - | 1.75 (14) | +10 (24) | 0.0 | 0/6 | |
| 48.4 (96.8) | 2.9 (23.2) | 15 (27) | - | - | 2/5 DD |
| 53.2 (106.4) | 1.93 (15.44) | 13 (29) | 9.0 | 6/6 | HNTD |
| 43.6 (87.2) | 1.6 (12.8) | 9 (29) | 7.0 | 6/6 | |
| 36.3 (72.6) | 1.31 (10.48) | 3 (29) | 5.1 | 6/6 | |
| 31.5 (63.0) | 1.14 (9.12) | 6 (28) | 4.4 | 6/6 | |
| 24.2 (48.4) | 0.88 (7.04) | 5 (19) | 2.0 | 2/6 | |

Td = 2.2 days; Time for control to reach 1 g = 17.8 days ; median tumor burden at start of therapy 210-260 mg ; CR = complete response ; IV = intravenous ; bwl = body weight loss at nadir ; (DT) = total dose ; HNTD = highest non-toxic dose ; lck = log¹⁰ cell kill.

Example 3

Taxotere was injected IV on days 14 and 25 post tumor implantation. Flavo was orally administered once a day from day 14 to 18 and from day 21 to 25.

FLAVOPIRIDOL (po) - DOCETAXEL (iv)
Prolonged exposure MA13/C

| Agent | Schedule | HNTD (DT) mg/kg | | % bwl (nadir) | Ick | Comments |
|--------------------------------------|-----------------------|--------------------|----------------------|------------------------------|------------|--------------|
| | | TXT | Flavo | | | |
| TXT Flavo | 14,25 14-18, 21-25 | 30 (60) | - 2.7 (27) | 3.6 (33) 11.6 (26) | 0.9 0.1 | HNTD HNTD |
| Combination TXT Combination Flavo | 14,25 14-18, 21-25 | 45 (90) | 4.5 (45) | 9.7 (19) | □5 | HNTC |

≈320 mg - tumor weight on day 14
(BCM-1252) - experiment no.

As in Example 2, the combination of docetaxel and repeated daily Flavo was found more active than either of the single agents, at equitoxic dosages. Synergy is shown by the log 4 increase in cells killed.

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

1. A pharmaceutical composition comprised of at least two constituents, wherein one constituent is Taxol®, Taxotere®, or derivatives thereof and the second constituent is a cyclin-dependent kinase.

5. 2. The pharmaceutical composition according to claim 1, wherein the cyclin-dependent kinase is flavopiridol.

3. A method of administering the constituents of the composition as claimed in any one of claims 1 or 2, wherein said administration is separate.

10 4. A method of administering the constituents of the composition as claimed in any one of claims 1 or 2, wherein said administration is separate and spaced out over time.

5. A pharmaceutical composition having therapeutic synergy in the treatment of neoplastic disease comprising Taxotere® and flavopiridol.

15 6. The pharmaceutical composition of claim 5, wherein the constituents of the composition are administered separately and spaced out over time.

7. The pharmaceutical composition of claim 5, wherein Taxotere® is administered on the first and last days of a ten day cycle and flavopiridol is administered on the first four days and last four days of said ten day cycle.

20 8. The pharmaceutical composition of claim 5, wherein Taxotere® is administered on days 14 and 23 and flavopiridol is administered on days 14 through 17 and days 20 through 23.

9. The pharmaceutical composition of claim 5, wherein the neoplastic disease is breast cancer.

25 10. The pharmaceutical composition of claim 5, wherein the neoplastic disease is lung cancer.

11. A method of administering the constituents of the composition as claimed in claim 2 wherein said constituents are administered separately and wherein flavopiridol is administered orally.

30 12. A method of administering the constituents of the composition as claimed in claim 2, wherein said constituents are administered separately and spaced out over time and wherein flavopiridol is administered orally.

13. The pharmaceutical composition of claim 5 wherein the flavopiridol is administered orally.

14. The pharmaceutical composition of claim 14 wherein Taxotere® is administered on days 14 and 25 and flavopiridol is administered orally on days 14 through 18 and days 21 through 25.

5 15. The pharmaceutical composition for treatment of neoplastic diseases wherein one constituent is Taxol®, Taxotere®, or derivatives thereof and the second constituent is flavopiridol, wherein said constituents are administered separately and spaced out over time and wherein said flavopiridol is administered orally.

10 16. The pharmaceutical composition of claim 14, wherein the neoplastic disease is breast cancer.

17. The pharmaceutical composition of claim 14, wherein the neoplastic disease is lung cancer.

18. The pharmaceutical composition of claim 16, wherein the neoplastic disease is breast cancer.

15 19. The pharmaceutical composition of claim 16, wherein the neoplastic disease is lung cancer.

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | WO 97 30174 A (SLOAN KETTERING INST CANCER ;SCHWARTZ GARY K (US); ALBINO ANTHONY) 21 August 1997 (1997-08-21) | 1-4, 15-19 |
| Y | page 126 -page 185; claims 15,17,32 | 1-19 |
| X | SCHWARTZ G K ET AL: "PHASE I TRIAL OF SEQUENTIAL PACLITAXEL AND CISPLATIN IN COMBINATION WITH THE CYCLIN DEPENDENT KINASE INHIBITOR FLAVOPIRIDOL (FLAVO) IN PATIENTS WITH ADVANCED SOLID TUMORS" CLINICAL CANCER RESEARCH, THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 5, no. SUPPL, November 1999 (1999-11), page 3754,AN122 XP001108950 ISSN: 1078-0432 | 1-4, 15-19 |
| Y | abstract --- -/- | 1-19 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | MOTWANI M ET AL: "SEQUENTIAL DEPENDENT ENHANCEMENT OF CASPASE ACTIVATION AND APOPTOSIS BY FLAVOPIRIDOL ON PACLITAXEL-TREATED HUMAN GASTRIC AND BREAST CANCER CELLS" CLINICAL CANCER RESEARCH, THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 5, no. 7, July 1996 (1996-07), pages 1876-1883, XP001113185 ISSN: 1078-0432 | 1-4, 15-19 |
| Y | abstract page 1882, column 2 | 1-19 |
| X | BIBLE K C ET AL: "CYTOTOXIC SYNERGY BETWEEN FLAVOPIRIDOL (NSC 649890, 186-8275) AND VARIOUS ANTINEOPLASTIC AGENTS: THE IMPORTANCE OF SEQUENCE OF ADMINISTRATION" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 57, 15 August 1997 (1997-08-15), pages 3375-3380, XP002128085 ISSN: 0008-5472 | 1,2 |
| Y | abstract page 3376, column 2 -page 3377, column 1 | 1-19 |
| X | MOTWANI M V ET AL: "DOCETAXEL AND NAVELBINE INDUCED APOPTOSIS IS ENHANCED BY FLAVOPIRIDOL (FLAVO) IN BREAST CANCER CELLS AND IS SEQUENCE DEPENDENT" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW YORK, NY, US, vol. 41, March 2000 (2000-03), page 143, AN912 XP008008541 ISSN: 0197-016X | 5-10,13, 14 |
| Y | abstract | 1-19 |
| Y | KELLAND L R: "FLAVOPIRIDOL, THE FIRST CYCLIN-DEPENDENT KINASE INHIBITOR TO ENTER THE CLINIC: CURRENT STATUS" EXPERT OPINION ON INVESTIGATIONAL DRUGS, ASHLEY PUBLICATIONS LTD., LONDON, GB, vol. 9, no. 12, December 2000 (2000-12), pages 2903-2911, XP008008516 ISSN: 1354-3784 page 2908; figure 2 | 1-19 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/04083

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 3,4,11 and 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/04083

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|-------------------------|
| WO 9730174 | A | 21-08-1997 | US 5821072 A 13-10-1998 |
| | | AU 2195297 A | 02-09-1997 |
| | | CA 2246734 A1 | 21-08-1997 |
| | | EP 0888458 A1 | 07-01-1999 |
| | | WO 9730174 A1 | 21-08-1997 |
| | | US 2001011076 A1 | 02-08-2001 |

